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Cost - minimization Analysis of Treprostinil vs. Epoprostenol as an Alternate to Oral Therapy: Non - responders for the Treatment of Pulmonary Arterial Hypertension

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ORIGINAL ARTICLE

Cost-minimization analysis of treprostinil vs. epoprostenol as an alternate to oral therapy non-responders for the treatment of pulmonary arterial hypertension

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ABSTRACT

Introduction: Idiopathic pulmonary arterial hypertension (IPAH) is associated with substantial morbidity and mortality. Treprostinil was compared to epoprostenol for the economic impact of treating IPAH patients who failed or were not candidates for bosentan.

Methods: The model was a cost-minimization analysis, assuming clinical equivalence was achieved by proper dosing of both drugs, in terms of survival and surrogate measures. Two theoretical cohorts of 270 patients were treated with subcutaneous treprostinil and intravenous epoprostenol, and were evaluated over 3 years using a spreadsheet model. Annual survival rates were estimated for the cohorts so that at endpoint 114 (42%) patients survived in both groups. The model utilized resource valuation data for medication and supply costs from Medicare; hospital, consultation, surgical, and diagnostic procedural fees from North Carolina hospitals; and costs to treat adverse events from published sources. Costs were obtained from standard lists and were presented as 2003 US dollars, discounted at 3%. Sensitivity analyses were performed testing all model uncertainties.

Results: In the base case analysis, treprostinil demonstrated savings of $22 701 and $37 433 per patient over 1- and 3-year time horizons, respectively. The greatest savings came from reduced or minimal hospitalizations attributed to the dose titration and treatment of adverse events, such as sepsis, associated with epoprostenol and its delivery system. Probabilistic sensitivity analyses resulted in average 3-year cost-savings of $41 051 (Standard Deviation = $13 902) per patient.

Conclusions: By initiating and continuing treatment with treprostinil over a 3-year period, the economic burden associated with IPAH may be reduced compared to treatment with epoprostenol. The greatest saving with treprostinil was attributed to decreased sepsis.

* At the time of analysis

Introduction

Pulmonary arterial hypertension (PAH) is a condition that is characterized by an increase in pulmonary vascular resistance (PVR) and an abnormally elevated mean pulmonary artery pressure (MPAP). The diagnosis of PAH is defined as a MPAP ≥ 25 mmHg at rest and a MPAP of ≥ 30 mmHg during exercise[1,2].

Idiopathic pulmonary arterial hypertension (IPAH) is estimated to have an annual incidence of 1–2 per million people in both the US and Europe[3]. That would provide an estimated 300–600 new cases of IPAH per year in the US. If left untreated, IPAH would lead to premature death. In one US study, the mean survival time was 2.8 years and the 5-year survival rate was 34%[4].

Treatment for IPAH is aimed at relieving symptoms, improving physical activity, and increasing survival[1]. The pharmacologic management of IPAH is usually initiated with the use of anticoagulants (e.g., warfarin) with or without diuretics for edema, and calcium channel blockers[1,3,5,6]. High-dose calcium channel blockers were the first treatments associated with an improved survival in IPAH[7].

If first-line treatment fails (i.e., there is no vasoresponsiveness or there is clinical worsening), endothelin receptor antagonist or prostaglandin treatment may be warranted, prior to a possible lung transplant. Endothelin receptor antagonists are vasodilators that act as mediators of the endothelin-1 receptors A and B[8,9]. Bosentan (Tracleer*) is currently the only endothelin receptor antagonist that is available in the United States and has been proven to be effective in the treatment of IPAH for patients having NYHA Class III or IV disease[10].

Prostacyclins are vasodilators with antiplatelet activity and have been reported to provide pulmonary vascular endothelial remodeling[6,7]. Epoprostenol (Flolan†) was the first prostacyclin approved by the FDA for the long-term intravenous treatment of idiopathic pulmonary hypertension (previously referred to as primary pulmonary hypertension) and for pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III or IV patients who do not respond adequately to conventional therapy[11]. Unfortunately, epoprostenol must be delivered via continuous intravenous (IV) infusion which is associated with septicemia, and incidents of interrupted line flow due to loss of line integrity that may include risks of pulmonary hypertension symptom rebound[12].

Treprostinil (Remodulin‡) represents a difference over previous prostacyclins in that it has an elimination half-life of 4.5 h and has been shown to be an effective treatment when administered via a continuous subcutaneous (SC) delivery[13,14]. United Therapeutics Corporation received FDA approval to market treprostinil for the long-term treatment of IPAH in patients with NYHA Class II, III, and IV disease who did not respond adequately to conventional therapy[15,16]. The SC delivery did not result in septicemia as a serious adverse event related to the drug delivery system, although actual comparison studies of the effect on safety or survival have not been conducted using subcutaneous delivery[12]. Treprostinil can be administered by a continuous IV administration for patients who are intolerant to subcutaneous administration[16]. However, the risks associated with intravenous epoprostenol would be assumed similar when using intravenous treprostinil.

The difference in route of administration and maintenance suggests that complications, hospitalizations and perhaps costs of delivery may be substantially different between treprostinil and epoprostenol. No studies, to our knowledge, have directly compared the costs of these two agents as part of a head-to-head economic evaluation. Highland and colleagues reported the results of a cost utility model of bosentan compared to both treprostinil and epoprostenol[17]. They reported that treatment with bosentan over a 1-year time horizon is cost-effective compared to both of the other treatments. However, the results were based on a number of assumptions, such as length of hospitalization and home care visits, which were not tested through sensitivity analyses. As well, the analysis was devoid of significant resource utilization parameters such as the cost per sepsis episode related to the delivery of epoprostenol. Therefore, the certainty of their results has not been definitively established.

The purpose of this study was to compare, by means of a pharmacoeconomic evaluation, the use of subcutaneous treprostinil and intravenous epoprostenol in the treatment of patients with NYHA Class III or Class IV IPAH who either have failed or were not candidates for bosentan therapy.

Methods

This economic evaluation was performed in compliance with the Canadian guidelines for economic evaluations of pharmaceuticals[18]. These guidelines are considered to be among the most stringent and prescriptive in the world, as they were developed to improve the quality and validity of economic studies[19,20]. The primary audiences for the findings of this study include the clinicians and health care providers who manage patient care.

* Tracleer is a registered trademark of Actelion Pharmaceuticals Ltd, Allschwil, Switzerland
† Flolan is a registered trademark of GlaxoSmithKline, Research Triangle Park, NC, USA
‡ Remodulin is a registered trademark of United Therapeutics Corporation, Silver Spring, MD, USA

The pharmacoeconomic approach was a cost-minimization analysis. This type of cost-effectiveness analysis considers only costs because effectiveness has been shown to be essentially equal between comparators[20]. This cost-minimization approach was undertaken as a result of equivalent survival data in NYHA Class III and IV patients treated with treprostinil and epoprostenol[21-23], evidence of successful transition from IV epoprostenol to SC treprostinil[24], successful treatment compared to placebo or conventional therapy and limitation in the use of a surrogate measure to compare equivalence, particularly when cardiopulmonary measures have been used as a surrogate to patient survival[12]. The analyses were conducted using a Microsoft Office Excel-based decision analytical model.

The time horizon chosen for this evaluation was 3 years. It was selected because the historical median survival time was 2.8 years, with a 5-year survival rate of 34%[4,25]. The 3-year time horizon allowed for the capture of relevant outcomes in the decision model. The model incorporated both the dose-titration phase in addition to maintenance therapy for patients with severe (NYHA classes III or IV) IPAH who had failed or were not candidates for bosentan therapy. These patients are candidates for long-term prostaglandin infusion or may receive this treatment as a bridge to lung or heart and lung transplantation.

In accordance with the pharmacoeconomic guidelines, the pharmacotherapy being evaluated must be compared to existing practice, i.e., the most prevalent clinical practice, and either the lowest cost comparator or the 'do-nothing' approach[18]. Treprostinil is indicated for the long-term, subcutaneous treatment of IPAH. Thus, the most appropriate comparator was epoprostenol, which is indicated for the treatment of IPAH in NYHA Class III and Class IV patients. Due to the severe nature of the disease, the 'do-nothing' approach was not considered appropriate.

The model followed two hypothetical cohorts of 270 patients receiving either SC treprostinil or IV epoprostenol. The model population was estimated using the US national population figures and the reported incidence rate of IPAH of 1–2 per million per year[3]. According to Rubin *et al.*[10], 60% of patients exposed to 125 mg of bosentan twice daily did not experience improvements in their condition in terms of WHO functional classes. Since endothelin antagonist treatment is aimed at improving IPAH symptoms, these patients may be considered candidates for prostacyclin treatment after failure with bosentan. To our knowledge, no data are currently available quantifying the proportion of newly diagnosed IPAH patients who would not be candidates for bosentan therapy and would require prostacyclin therapy. Sixty percent of the 450 newly diagnosed patients each year were estimated to be candidates at some point in time for IV epoprostenol or SC treprostinil. This proportion probably overestimates the number of failures with bosentan therapy, but compensates for the lack of precise estimates of the number of patients who are not candidates for endothelin antagonist therapy.

The spreadsheet model was designed to represent the logical sequence of clinical practice as described in the literature and verified by expert clinical opinion. In the model, each patient underwent a dose fixing/titration phase in addition to receiving maintenance therapy. Survival was also taken into account by applying to both drug arms a probability of 88%, 76%, and 63% for the first, second and third years respectively[12]. An initial cohort size of 270 patients was used for calculations (i.e., 60% of 450 new cases), where 221 and 188 patients survived to mid-points of year 2 and year 3, upon which calculations were performed. One hundred and fourteen patients (42%) were assumed to be alive at the end of the model.

Resource utilization data were derived from the available literature in the form of clinical trials and published treatment guidelines. Expert clinical opinion was used to confirm the resource utilization data extracted and to provide guidance in areas of uncertainty for further testing in sensitivity analyses.

Drug costs were taken from Medicare lists. SC treprostinil dosing was based on a 1:1 ratio compared to IV epoprostenol[24]. Treprostinil is currently supplied in various concentrations with the most relevant to this study being the 2.5 mg/mL concentration, with a Medicare cost of $49.40 (i.e., 80% of $61.75) per mg. An average weight of 70 kg per patient was used in the calculations.

Epoprostenol is administered via continuous intravenous infusion. Due to its short half-life of 3–5 min[7], and the potential for prostacyclin-related adverse events, epoprostenol therapy requires that patients be hospitalized for a period of 5–7 days in order to titrate the dose of the drug to an effective maintenance level. Treatment is usually initiated at 2–4 ng/kg/min with a target dose of 10–15 ng/kg/min in 2–4 weeks[26]. The mean dose in adults is approximately 20–40 ng/kg/min[27], which for a 70 kg patient would be 25 ng/kg/min or a daily dose of 2.5 mg[24]. Each vial contains 1.5 mg, with the Medicare cost per mg of epoprostenol being $24.08 (i.e., 80% of $30.10).

Daily medication costs were determined based on the number of units required for each daily dose. The daily medication cost for epoprostenol also included the cost of the proprietary glycol-buffered diluent required to prepare the medication. Reimbursement rates for both the drug delivery system and required infusion supplies for treprostinil and epoprostenol were obtained from Medicare lists.

Medical consultation fees were derived from hospital charge lists within the state of North Carolina. All patients incurred the cost of an initial consultation with their family practitioner, for referral to their specialist, regardless of the treatment. Experts were consulted to establish the type and frequency of visits that patients would require, according to the treatment. Regardless of the treatment, patients were assumed to have a yearly consultation with a cardiologist and a reassessment visit every 3 months. According to expert clinical opinion, no other specialists would normally be consulted in the treatment of IPAH.

In addition to visits for specialists' consultations, medical visits also include a nurse's time to train patients to administer the drug. Before discharge of patients whose drug dose was being titrated, both the patient and a spouse or close relative would receive training from a specially trained nurse on proper intravenous or subcutaneous catheter care, sterile techniques, and drug preparation/administration. The time spent on training was two daily 15-min sessions for treprostinil and five daily 15-min sessions for epoprostenol.

Costs for surgical and diagnostic procedures were also derived from North Carolina hospital charge lists. Epoprostenol requires the surgical placement of an intravenous catheter. Treprostinil does not require that such a procedure takes place. Thus, in the model, all patients treated with epoprostenol would incur this cost. Total costs for other diagnostic procedures were based on the frequency of performing each assessment and the proportion of patients who require the procedure and were taken from the literature[2,28]. Utilization rates for diagnostic procedures were verified via expert clinical opinion.

Because of the route of infusion, patients receiving IV epoprostenol are at risk for sepsis and intravenous line infections[12]. For this reason, costs involved with treating sepsis were determined. Estimates from the literature were used, and they are presented as the mean cost per episode.

Utilization rates for hospitalization were also determined from the literature[2,29]. Each listed reference presented data from several sources. Costs varied slightly according to the source, however, the valuations were similar for all reported resources. Hospital charge lists from North Carolina were used to determine the cost of hospitalizations.

The following assumptions were applied in the economic analysis. The main assumption was a dose adjustment factor of 1:1 (treprostinil:epoprostenol) [24], and assuming an average length of hospital stay for dose titration of 5 days for epoprostenol and 1 day for treprostinil. The dose adjustment factor was then varied from 0.82:1 to 1.18:1 and the average length of stay was varied from 0–2 days for treprostinil and from 2–10 days for epoprostenol. Each assumption was determined through either a literature review or from expert clinical opinion. The uncertainty inherent in each assumption was tested in a variety of pre-defined sensitivity analyses. All assumptions used in this economic evaluation are presented in Table 1.

Reported costs and savings were on a per patient basis for the first month of treatment, after 1 year and after 3 years of treatment. Patient costs were derived from the total cohort cost for the specific period and divided by the cohort size at the beginning of that period.

Sensitivity analyses were performed to determine the robustness of our model to various parameters and assumptions. Each one-way sensitivity analysis and the corresponding parameter values tested are presented in Table 2. Multivariate sensitivity analyses were performed on population estimates using 10 000

Table 1. *List of assumptions used in the economic analysis*

Assumption	Description	Valuation
Dose adjustment factor	The dose ratio (treprostinil:epoprostenol) chosen for the analysis was based on the maintenance dose reported in a transition study of eight IPAH patients treated with epoprostenol who switch to treprostinil[24]	1:1
Duration of hospitalization to titrate medication to an appropriate dose	Estimated via clinical expert opinion to be 1 day for treprostinil and 5 days for epoprostenol	Treprostinil – 1 day; Epoprostenol – 5 days
Rate of sepsis	Estimated from the reported rate provided in a long-term follow-up study on patients treated with epoprostenol[12]	0.14 per person-year
Rate and length of stay for re-hospitalizations	Based on reported values in a multinational, prospective economic evaluation of epoprostenol. Treprostinil rates were adjusted using the reported epoprostenol rates minus reported rates for adverse events such as sepsis, and other events associated with the epoprostenol drug delivery system	Treprostinil – 10.2 days/year; Epoprostenol – 15 days/year
Cost per episode of sepsis	Based on a study reporting the average cost to treat severe sepsis and sepsis shock[32]. The reported value adjusted using the health care portion of the CPI	$28 500 per episode

Table 2. Parameter values tested in one-way sensitivity analyses

Parameter	Base case value	Sensitivity values	Distribution and parameters for multivariate analyses	Reason for range
Discount rate	3%	0–5%	Normal, mean: 3%; SD: 1%	As per CCOHTA guidelines[18]
Dose adjustment factor	1:1	0.82:1–1.18:1	Triangular, lkeliest value: 1:1	As per rates reported in the literature[24,33]
Hospitalization to titrate medication	Treprostinil – 1 day; Epoprostenol – 5 days	Treprostinil: 0–2 days; Epoprostenol: 2–l0 days	Normal, mean: 1.0; SD: 0.3; Weibull, location: 3; Scale: 3; Shape: 2	Range provided by expert opinion
Rate of sepsis	0.14/person-year	0.07–0.32/person-year	Lognormal, mean: 0.14; SD: 0.04	Estimated range to test
Rate and length of stay for re-hospitalizations	Treprostinil – 10.2 days/year; Epoprostenol – 15 days/year	Treprostinil: 5.1–20.4 days/year; Epoprostenol: 7.5–30 days/year	Weibull, location: 7.5; Scale: 10; Shape: 2	As per standard deviation reported in prospective economic evaluation[31]
Cost to treat sepsis	$28 500/episode	$14 250–$42 750/episode	Lognormal, mean: $28 500; SD: $3000	Estimated range of ± 50%

probabilistic Monte-Carlo simulations on Crystal Ball 2000 v5.2 software to determine the robustness of our model to multiple variations in parameter estimates. Sepsis cost and rates were assigned a log-normal distribution while other empirical probability variables were assigned normal or Weibull distributions. Variables without a known distribution (based on assumptions or published ranges) were assigned a triangular distribution. The parameters and probability distributions used in the multivariate sensitivity analyses are presented in Table 2.

Results

A cohort of 270 patients in each arm, who had previously failed or were not candidates for bosentan, was followed over a 3-year period. Survival was the same in both groups (42%) over the 3 years. Thus, the final size was 188 in both the epoprostenol and treprostinil arms.

Resource costs and utilization rates used in this economic evaluation are presented in Table 3. Included in this table is the estimated $28 500 cost of treating an episode of sepsis[30]. This value was determined by pro-rating the estimated cost to 2003 USD by using the health portion of the consumer price index. Hospital utilization and valuation data are presented in Tables 4 and 5, respectively.

All results are reported in 2003 USD, discounted at a 3% rate. Results through the first 3 years of prostacyclin therapy are presented in Table 6, along with itemized costs for SC treprostinil and IV epoprostenol. The total expected cost of treprostinil therapy was $18 640, $100 303, and $294 193 per patient at 1 month, 1 year, and 3 years, respectively. The total expected costs in the epoprostenol arm were $32 907, $123 005, and $331 625 per patient, respectively. A significant contributor to the cost of epoprostenol was the resource use within the hospital both for dose titration and subsequent hospitalization for adverse drug reaction other than sepsis. Hospitalization costs represented approximately 20% of the resource utilization for epoprostenol therapy.

Results of the base case analysis are presented in Table 7. The total expected cost savings in favor of treprostinil were $14 266, $22 701, and $37 433 per patient for 1 month, 1 year, and 3 years, respectively. The expected average cost-saving per patient per year was $12 478. The cost-savings results were impacted by the difference in hospital resource use between the two drugs. The total hospitalization cost, including the resource use to treat sepsis, over the 3-year period was $39 377 for treprostinil and $76 525 for epoprostenol.

Sensitivity analyses

Since the analysis was based on the assumption of a 1:1 dose ratio, that ratio was varied while all other variables were held constant. The result was that the model was sensitive to the range of dosing for treprostinil. The cost-savings decreased as the dose adjustment ratio approached 1.18:1. In addition, since the hospitalizations were a driving component in both the cost of epoprostenol and the expected cost-saving, hospitalization rates were varied

Table 3. *Medication resource utilization in patients with pulmonary hypertension*

Medication	Resource utilization	Valuation per unit ($USD)
Medication and medical equipment*		
Treprostinil	2.05 mg/day	$49†
Epoprostenol	2.50 mg/day	$24†
Diluent	2.5 vials per day	$11†
Treprostinil infusion pump and supplies	100%	$21/day†
Epoprostenol infusion pump and supplies	100%	$39/day†
Medical consultations and visits‡		
General physician	Yearly	$134
Cardiologist		
Consultation	Yearly	$537
Subsequent visits	Each 3 months	$193
Training nurse	Treprostinil – two session‡, epoprostenol – five sessions‡	$85
Laboratory and diagnostic procedures‡		
Echocardiogram	Every 6 months	$190
Right heart catheterization	Every 12 months plus once at initiation of therapy with epoprostenol	$5138
Pulmonary angiogram	n/a	$1949
Exercise stress test – 6 min walk	Every 3 months	$944
Chest radiography	Yearly	$241
Thorax CT scan	One time only at initiation	$1569
Oxygen consumption studies		
Simple spirometry	Every 12 months	$165
Lung compliance	Every 12 months	$73
Blood-gas analysis	Every 12 months	$161
Oxygen saturation (with 6-min walk)	Every 3 months	$39
Blood cultures – CBC	Every 3 months	$115
Chemistry panel	Every 3 months	$220
PTT	Every 3 months	$92
INR	Every 3 months	$96
BNP	Every 3 months	$196
Digoxin level	Every 12 months	$131
Surgical procedures‡		
Hickman or Broviac CVC	0% – treprostinil, once yearly – epoprostenol	$1054
Removal of CVC	0% – treprostinil, once yearly – epoprostenol	$726
Adverse events		
Sepsis§	0% – treprostinil, 14% – epoprostenol	$28 500[32]

BNP – brain naturetic peptide; CBC – complete blood counts; CT – computerized tomography; CVC – central venous catheter; LHC – left heart catheterization; MRI – magnetic resonance imaging; RHC – right heart catheterization
*The source of utilization was the manufacturer
†Medicare unit price; provided by manufacturer
‡The source of utilization was Schulman, 1996[28]; BCSG, 2001[2] with Kathy Hague, RN, 2003-10-07
§As per McLaughlin *et al.* 2002[12], confirmed by Kathy Hague, RN, 2003-10-07
N.B.: All numbers rounded to nearest dollar

Table 4. *Probability of hospitalizations by treatment type*

Hospitalizations	Probability of utilization	
	Treprostinil	Epoprostenol
Length of stay for dose titration phase*	1 day	5–7 days – dose titration
Length of stay for re-hospitalizations†	15 days	15 days
Probability per year of re-hospitalizations*	0.68 admissions per year‡	1.0 admissions per year

*Utilization rates were determined from the standard admission and therapy initiation protocols from the University of Cleveland Hospitals as provided by Kathy Hague, RN, 2003-10-07
†Derived from Schulman *et al.*, 1996[31]
‡Derived from epoprostenol rate minus the adverse event rates associated with the epoprostenol drug delivery system, i.e., sepsis, loss of line integrity, etc.[29]

Table 5. *Hospitalization valuations (2003 $USD) and required adjustments*

Parameter	Cost*
Cost per intensive care unit day	$850
Cost per general ward day	$265
Emergency room	$380

*Does not include the cost of monitoring

while maintaining all other variables constant. However, the cost-savings remained at all ranges of hospitalizations. Results of the one-way sensitivity analyses are presented in Table 8.

Results of the multivariate sensitivity analyses, presented in Table 9, were consistent with both the base case and one-way sensitivity analyses. In the first year of treatment treprostinil was cost-saving in all cases. It produced cost-savings in > 99% of all scenarios

Table 6. *Itemized costs per patient for treprostinil and epoprostenol*

Item	Treprostinil			Epoprostenol			Average savings per year
	1 month	1 year	3 years	1 month	1 year	3 years	
Drug and administration	$3759	$49 377	$146 743	$2658	$34 914	$103 760	$14 328
Equipment	$636	$8348	$24 810	$1187	$15 593	$46 340	–$7177
Medical visits	$1378	$7623	$21 194	$3781	$12 948	$31 168	–$3325
Medical procedures	$11 396	$21 338	$62 068	$17 588	$29 260	$73 832	–$3921
Hospitalization	$1472	$13 617	$39 377	$7360	$25 922	$63 545	–$8056
AE – sepsis	$0	$0	$0	$333	$4368	$12 980	–$4327
Total expected cost	$18 640*	$100 304	$294 193	$32 907	$123 005	$331 625	–$12 478

AE – adverse events
*Items may not sum to total cost due to rounding

Table 7. *Base case savings with treprostinil treatment compared to epoprostenol*

Drug	1 month	1 year	3 years
Per cohort (270 patients)			
Treprostinil	$5 032 926	$24 102 931	$63 708 269
Epoprostenol	$8 884 843	$29 558 005	$72 172 498
Incremental savings	$3 851 917	$5 455 074	$8 464 229
Per patient			
Treprostinil	$18 640	$100 303	$294 192
Epoprostenol	$32 907	$123 005	$331 625
Incremental savings	$14 266	$22 701	$37 433

Table 8. *Results of one-way sensitivity analyses*

Parameter adjusted	Total savings per patient of treprostinil over epoprostenol	
	After 1 year	After 3 years
Base case*	$22 701	$37 433
Discount rate		
0–5%	$22 020–$23 179	$35 670–$38 701
Dose adjustment factor†		
0.82:1–1.18:1	$31 589–$13 813	$63 846–$11 019
Cost of sepsis per episode		
$14 250–$42 750	$20 517–$24 885	$30 943–$43 923
Sepsis rate		
0.07–0.32	$18 737–$32 895	$25 311–$68 601
Dose titration days		
Epoprostenol: 2–10 days	$15 720–$34 337	$30 451–$49 068
Treprostinil: 0–2 days	$25 028–$20 374	$39 760–$35 105
Average length of re-hospitalization		
7.5–30 days	$18 650–$30 804	$24 620–$63 058

*Discount rate = 3%
†Ratio between average treprostinil and epoprostenol dose

when compared with epoprostenol over the 3-year time horizon. The savings over 3 years were $15 479 757 (SD: $4 995 797 [–$438 698 to $32 561 707]), or approximately $41 051 (SD: $13 902 [–$104 to $92 679]) per patient per year.

Table 9. Results of Monte-Carlo simulations

Statistic	Total savings per patient of treprostinil over epoprostenol		
	1 month	1 year	3 years
Mean	$15 596	$24 897	$41 051
Median	$15 281	$24 766	$40 898
Standard deviation	$2910	$5559	$13 902
Range minimum	$8668	$8545	–$104
Range maximum	$29 483	$45 442	$92 679
Mean standard error	$180	$359	$1014
Percentile cost savings	100th	100th	> 99th

Discussion

In the base case analysis, treating the cohort with treprostinil resulted in cost savings over the first 3 years of treatment of more than $8 million. On a per patient basis, the cost-saving was $37 433. Hence, SC treprostinil appears to be cost-saving compared to treatment with IV epoprostenol under a wide range of assumptions.

The driver for those savings was the avoidance of hospitalization associated with the titration of epoprostenol and the avoidance of sepsis that occurs with the mode of administration of epoprostenol. The expected resource utilization for hospitalization and side-effect therapy in the epoprostenol cohort was nearly twice that in the treprostinil cohort.

The model results were sensitive in magnitude but not in direction to scenarios including varying the average length of hospital stay during the titration of epoprostenol and varying the rates of hospitalizations. In both cases, the most conservative estimates, i.e., estimates which may have been biased against treprostinil were congruent with the cost savings presented in the base case. The model was sensitive to the dose-adjustment factor used to determine an appropriate dose of treprostinil compared to epoprostenol. Varying the effective transitioning dose adjustment factor from 0.82:1[24] to an overly conservative value of 1.18:1 resulted in cost savings after the first 3 years of treatment.

The Monte Carlo multivariate simulations produced results similar to what was determined through the one-way sensitivity analyses. The probability of incremental cost-savings by using treprostinil during the first 3 years of treatment was over 99%.

The only other comparable economic evaluation was the study by Highland and coworkers, comparing bosentan, epoprostenol, and treprostinil[17]. That study reported that the expected cost increases of SC treprostinil compared to IV epoprostenol over a 1-year period was $1 241 900 for a cohort of 100 patients or $12 419 per patient. However, the present study estimated that the expected cost savings were $5 455 074 for 240 patients over the first year or $22 701 per patient. The difference in outcomes may be attributed to the assumptions used to conduct the two analyses. In this study, the rate of hospitalizations for epoprostenol was estimated from the literature and verified through expert clinical opinion. In the Highland study, hospitalizations were assumed to be equal, which is inconsistent with the clinical management patterns associated with the two drugs. Both the hospitalization days required to ensure treatments are properly titrated and patients are properly trained on how to administer their treatments, and the re-hospitalizations due to various adverse events, e.g., sepsis, suggest the hospitalizations are fewer for treprostinil compared to epoprostenol. In addition, the dose assumptions that were utilized were derived from early dosing studies and do not reflect recent comparative dose studies[24]. Unfortunately, no sensitivity analyses, either single or multivariate, were performed to test the impact of these assumptions. Thus, the assumptions driving the cost portion of that cost-effectiveness study were not tested to determine the robustness of their model to different scenarios. As a result, the assumptions on which the results were derived may have been biased in favor of epoprostenol.

The only other cost study was a prospective cost analysis of epoprostenol[31]. That cost analysis was performed in patients with congestive heart failure and included the cost of hospitalization. Length of hospital stay was the most influential cost driver in the group of patients treated with epoprostenol; however, the proportion of the total cost of epoprostenol treatment could not be determined.

Limitations

As with any economic analysis, certain limitations were inherent in this evaluation. The base case analysis did not include the cost of pain management for each treatment. The actual cost of pain management could not be captured accurately; thus, it did not seem prudent to include that assumption in our base case analysis. However, a post-hoc analysis was performed to assess the cost of site pain management related to the use of treprostinil. According to expert clinical opinion, a cost of $100 per patient per month can be assigned. This results in slightly reduced savings over 3 years, at $33 529 per patient. Assigning costs to pain management only to treprostinil is biasing against this treatment, and even in that case, the strategy was still cost-saving.

Another possible source of error was the mortality rate, which was calculated on a yearly basis. Thus, the probability of mortality was distributed along a linear equation, which may not be the case. However, this method for incorporation of mortality rates was performed for both treatments. The distribution along a linear equation decreased the complexity of the model without introducing any bias into the analysis.

Costs for surgical and diagnostic procedures were derived from hospital charge lists. These charges may fluctuate, but we assumed that those fluctuations would equally apply to both drug groups and would not change the direction of results. These assumptions do not take into consideration the possibility of having the differences in results narrowed due to this approach.

Also, it is common practice in pharmacoeconomic studies to use data from a particular region as a proxy for a larger one. In a country like the United States, the cost of care can vary greatly from one state to another. This can yield an overestimation in certain parts of the country but underestimation in other parts. Overall, it can be considered as a reasonably good estimate of expected results using a national average for costs. While variations in the costs may influence the magnitude of the therapies' costs on a per cohort and per patient basis, incremental savings should remain in the same range as those presented in this study, since an inflation or deflation of the resources' costs is most likely to be equivalent in both treatment arms.

Finally, it is important to take into account that the results of the present study apply only to the subcutaneous delivery of treprostinil compared to the intravenous delivery of epoprostenol. As of November 24, 2004, the FDA approved intravenous dosing of treprostinil, for the following indication: treprostinil 'is indicated for the continuous subcutaneous or intravenous infusion (for patients unable to tolerate a subcutaneous infusion) for the treatment of pulmonary arterial hypertension in patients with NYHA Class II–IV symptoms to diminish symptoms associated with exercise'[16].

While no study has been performed to compare the two medications when delivered through a central venous catheter, it is believed that the administration costs and the risks associated with intravenous therapy would be similar between the two intravenous formulations. However, it is worth noting that there are four strengths of SC treprostinil vials, which offers flexibility in dosing, and each multi-dose vial can be used for up to 30 days at ambient room temperature after the initial vial entry. On the other hand, IV epoprostenol is available as single-use dose with two strengths, and must be reconstituted and used within 24 h.

Conclusion

Based on a cost-minimization analysis, treprostinil is more resource efficient with treatment providing cost-savings over a 3-year period. The greatest cost-savings were attributed to a decrease in the average length of hospital stay, as treprostinil does not require the level of dose titration and training of patients that is needed for the proper administration of epoprostenol. Additionally, cost-savings from the use of treprostinil may also be attributed to fewer hospitalizations as a result of the absence of adverse events, especially septicemias that are associated with the intravenous administration of epoprostenol.

The expected average savings due to the use of treprostinil was determined to be $12 478 per patient per year over 3 years.

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References

1. Pass S, Dusing M. Current and emerging therapy for pulmonary hypertension. Ann Pharmacother 2002;36:1414-23
2. British Cardiac Society Guidelines and Medical Practice Committee. Recommendations on the management of pulmonary hypertension in clinical practice. Heart 2001;86:i1-i13
3. Gaine S, Rubin L. Primary pulmonary hypertension. Lancet 1998;352:719-25
4. D'Alonzo G, Barst R, Ayres S, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343-9
5. Rich S. Primary pulmonary hypertension. Curr Treat Options Cardiovasc Med 2000;2:135-40
6. Rich S. Medical treatment of primary pulmonary hypertension: a bridge to transplantation? Am J Cardiol 1995;75:63A-6A
7. Gildea T, Arroliga A, Minai A. Treatments and strategies to optimize the comprehensive management of patients with pulmonary arterial hypertension. Clevel Clin J Med 2003;70: S18-S27
8. Channick R, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001;358:1119-23
9. Chen SJ, Chen YF, Meng QC, Durand J, Dicarlo VS, Oparil S. Endothelin-receptor antagonist bosentan prevents and reverses hypoxic pulmonary hypertension in rats. J Appl Physiol 1995;79:2122-31
10. Rubin L, Badesch D, Barst R, et al. Bosentan therapy for pulmonary arterial hypertension. New Engl J Med 2002;346: 896-903

11. FDA. Flolan approval letter. 2000. http://www.fda.gov/cder/foi/nda/2000/20-444S003_Flolan_Approv.pdf [accessed June 15, 2005]
12. McLaughlin V, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106:1477-82
13. Simonneau G, Barst R, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002;165:800-4
14. McLaughlin VV. Improvement in exercise tolerance with treprostinil is dose related for pulmonary arterial hypertension. American Thoracic Society (ATS) 2002 International Conference; 1-2, 2002
15. FDA. Remodulin approval letter. 2002. http://www.fda.gov/cder/foi/nda/2002/21-272_Remodulin_Approv.pdf [accessed June 2005]
16. United Therapeutics Corporation. Product monograph: Remodulin [treprostinil sodium] injection. 2004
17. Highland K, Strange C, Mazur J, Simpson K. Treatment of pulmonary arterial hypertension: a preliminary decision analysis. Chest 2003;124:2087-92
18. Canadian Coordinating Office for Health Technology Assessment. Guidelines for economic evaluation of pharmaceuticals: Canada, 2nd ed. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1997
19. Jacobs P, Bachynsky J, Baladi J. A comparative review of pharmacoeconomic guidelines. Pharmacoeconomics 1995; 8:182-9
20. Torrance G, Blaker D, Detsky A, et al. Canadian guidelines for economic evaluation of pharmaceuticals: Canadian collaboration workshop for pharmacoeconomics. Pharmacoeconomics 1996;9:535-59
21. Gibbs JS. Chronic infusion of treprostinil is safe, and appears to prolong survival over a three-year period in patients with pulmonary arterial hypertension. American Heart Association (AHA) Scientific Sessions 2002; 1-3, 2002
22. Shapiro S, Oudiz R, Cao T, et al. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. J Am College Cardiol 1997;30:343-9
23. Barst R, Rubin L, McGoon M, Caldwell E, Long W, Levy P. Survival of primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Intern Med 1994;121:409-15
24. Vachiery J, Hill N, Zwicke D, Barst R, Blackburn S, Naeije R. Transitioning from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. Chest 2002;121:1561-5
25. Rich S, Dantzker R, Ayres S, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987;107:249-23
26. Galie N, Manes A, Branzi A. Medical therapy of pulmonary hypertension. The prostacyclins. Clin Chest Med 2001;22:529-37
27. Widlitz A, Barst R. Pulmonary arterial hypertension in children. Eur Respir J 2003;21:155-76
28. Schulman K, Glick H, Buxton M, et al. The economic evaluation of the FIRST study: design of a prospective analysis alongside a multinational phase III clinical trial. Control Clin Trials 1996;17:304-15
29. Banayan D, Witt J, McCarthy M, Granton JT. The direct and indirect costs of chronic intravenous epoprostenol in patients with pulmonary arterial hypertension. ATS 99th International Conference,16-5-2003
30. Angus D, Linde-Zwirble W, Lidicker J, Clermont G, Carcillo J, Pinksy M. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303-10
31. Schulman K, Buxton M, Glick H. Results of the economic evaluation of the FIRST study. Int J Tech Assess Health Care 1996;12:698-713
32. Teres D, Rapoport J, Lemeshow S, Kim S, Akhras K. Effects of severity of illness on resource use by survivors and nonsurvivors of severe sepsis at intensive care unit admission. Crit Care Med 2002;30:2413-9
33. Anon. Treprostinil (Remodulin) for pulmonary arterial hypertension. Med Lett 2002;44:80-2

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